Real-time Volumetric Assessment of the Human Carotid Artery: Handheld Multispectral Optoacoustic Tomography

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Abstract: Background Multispectral optical imaging has the capability of resolving hemoglobin, lipid, and water. Volumetric multispectral optoacoustic tomography (MSOT) is a hybrid imaging technique that provides a unique combination of functional and molecular contrast with real-time handheld imaging. Purpose To investigate whether volumetric MSOT can provide real-time assessment of the anatomic and functional status of the human carotid artery bifurcation noninvasively. Materials and Methods Imaging of healthy volunteers (n = 16) was performed with a custom-designed handheld volumetric MSOT scanner capable of high-spatial-resolution (approximately 200 µm) and real-time (10 volumes/sec) three-dimensional imaging, while further providing spectroscopic capacity through fast tuning of the excitation light wavelength. For comparison and anatomic cross-validation, volunteers were also scanned with clinical B-mode US. Results Volumetric MSOT achieved real-time imaging and characterization of the entire carotid bifurcation area across three dimensions simultaneously captured in a single volumetric image frame. Analysis of the acquired data further showed that a higher contrast-to-noise ratio can be achieved for wavelengths corresponding to a high optical absorption of oxygenated hemoglobin. Conclusion The human carotid artery was visualized by using handheld volumetric multispectral optoacoustic tomography. This imaging approach is less prone to motion artifacts than are the conventional clinical imaging methods, holding promise for providing additional image-based biomarkers for noninvasive label-free assessment of carotid artery disease.

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Conflicts of interest are listed at the end of this article.

See also the editorial by Mezrich in this issue.

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Background: Multispectral optical imaging has the capability of resolving hemoglobin, lipid, and water. Volumetric multispectral optoacoustic tomography (MSOT) is a hybrid imaging technique that provides a unique combination of functional and molecular contrast with real-time handheld imaging.

Purpose: To investigate whether volumetric MSOT can provide real-time assessment of the anatomic and functional status of the human carotid artery bifurcation noninvasively.

Materials and Methods: Imaging of healthy volunteers (n = 16) was performed with a custom-designed handheld volumetric MSOT scanner capable of high-spatial-resolution (approximately 200 μm) and real-time (10 volumes/sec) three-dimensional imaging, while further providing spectroscopic capacity through fast tuning of the excitation light wavelength. For comparison and anatomic cross-validation, volunteers were also scanned with clinical B-mode US.

Results: Volumetric MSOT achieved real-time imaging and characterization of the entire carotid bifurcation area across three dimensions simultaneously captured in a single volumetric image frame. Analysis of the acquired data further showed that a higher contrast-to-noise ratio can be achieved for wavelengths corresponding to a high optical absorption of oxygenated hemoglobin.

Conclusion: The human carotid artery was visualized by using handheld volumetric multispectral optoacoustic tomography. This imaging approach is less prone to motion artifacts than are the conventional clinical imaging methods, holding promise for providing additional image-based biomarkers for noninvasive label-free assessment of carotid artery disease.

Online supplemental material is available for this article.

Most ischemic strokes are associated with carotid artery disease originating from the bifurcation area (1,2). Methods for visualizing human carotids include duplex US (3), CT (4), and MRI (5). However, rapid characterization of tissue function and molecular composition is limited with these modalities. Recently, intravascular optical imaging approaches assisted with smart fluorescence molecular agents have demonstrated powerful performance in detecting specific atherosclerotic biomarkers, including inflammation, protease upregulation, lipid content in areas of high endothelial permeability, and vascular cell adhesion molecules (6–9). Yet fluorescence-based methods can at best provide a qualitative indication of the existence of biomarker activity, rather than an accurate assessment of its biodistribution.

Optoacoustic imaging provides unique opportunities for accurate diagnostics and assessment of carotid artery disease. To this end, the technique has been used in diverse angiographic applications and enabled multiscale imaging of vascular structures ranging from capillaries to major vessels, including cross-sectional (two-dimensional) carotid imaging, at depths of several millimeters to centimeters in living tissues (10–12). Multispectral optoacoustic tomography (MSOT) can further provide valuable functional information by spectroscopically identifying the presence of specific tissue chromophores and extrinsic agents (13) or evaluation of physiologic conditions with label-free mapping of blood oxygen saturation in tissues (14). MSOT imaging of matrix metalloproteinase activity, typically associated with atherosclerotic plaque instability, has been demonstrated in ex vivo human carotid plaque samples (15). By using excitation in the wavelength range of 1210 nm, corresponding to the peak optical absorption by lipids, optoacoustic imaging could clearly identify and characterize plaques within human aorta and carotid artery samples ex vivo (16,17).

The goal of this study was to investigate whether optoacoustic imaging can be used clinically to provide three-dimensional assessment of anatomic and functional status of the entire bifurcation area of the human carotid artery

Abbreviation

MSOT = multispectral optoacoustic tomography

Summary

Volumetric multispectral optoacoustic tomography can provide three-dimensional assessment of anatomical and functional status of the entire bifurcation area of the human carotid artery noninvasively, in real time, and in three dimensions.

Key Points

- Volumetric multispectral optoacoustic tomography allowed spectroscopic volumetric characterization of the carotid artery and was less prone to motion artifacts than were the conventional US methods used in clinical practice.
- This new imaging modality holds promise for noninvasive functional assessment of clinically relevant biomarkers of cardiovascular disease.

noninvasively and in real time, thus addressing limitations of the existing imaging approaches used for the characterization of carotid artery disease.

Materials and Methods

We devised a handheld volumetric MSOT system to enable noninvasive, real-time, three-dimensional visualization of human carotids (Fig 1, *A*). It features spherical array detection geometry with nearly isotropic three-dimensional resolution of 200 μm (18), wide tunability of the excitation light in the range of 680–950 nm, and parallel data acquisition for real-time imaging at a volumetric frame rate up to 100 Hz. The laser further features a separate output delivering the fundamental pumping wavelength of 1064 nm. The detection array was attached to a holder containing a liquid acoustic coupling medium (water) sealed with a transparent membrane (Fig 1, *A*). The images were rendered in a volume of $20 \times 20 \times 20$ mm^3 ($200 \times 200 \times 200$ voxels) and then cropped along the depth (or *z*) axis for better visualization of the carotid artery. Graphics processing unit–based implementation of the reconstruction procedure allowed for a live preview of the three-dimensional optoacoustic images (19). All processing steps were performed in Matlab (version 9.1, R2016b; MathWorks, Natick, Mass). Image visualization and analysis were performed in Amira (Zuse Institute, Berlin, Germany).

For this preliminary study, no institutional review board approval was required as set out for noninterventional human studies by the German Drug or Medical Device Act. Healthy volunteers consisting of female and male researchers (age range, 22–44 years) with no history of cardiovascular diseases were recruited between April 2017 and November 2018. Written informed consent was obtained from all volunteers. Exclusion criteria were physical or mental conditions inhibiting volunteers from making informed judgements, history of cardiovascular disease, pregnancy, or breastfeeding. The final cohort consisted of 16 healthy volunteers with mean age ± standard deviation of 29.75 years ± 5.55 (nine of 16 [56.25%] women with mean age of 28 years ± 2.66; seven of 16 [43.75%] men with mean age of 32 years ± 7.23). All volunteers consented to be imaged with the handheld volumetric MSOT probe in full accordance with the work safety regulations of the Helmholtz Centre Munich (Neuherberg, Germany). The pulse repetition rate of the laser was set to 10 Hz while the maximal light fluence on the skin surface was maintained below 20 mJ/cm^2 in the range of 730–900 nm and below 50 mJ/cm^2 at 1064 nm to fulfill the safety exposure limits (20) for nanosecond laser radiation in the entire wavelength range used in our experiments. All volunteers were imaged at wavelengths of 850 nm and 1064 nm for optimal visualization of the carotid artery. Five volunteers (three women [60%] with mean age of 26.6 years ± 3.3; two men [40%] with mean age of 40.5 years ± 3.5) were also imaged between 730–900 nm for multispectral evaluation. The acquired volumetric MSOT images of two volunteers (two women with mean age of 28.5 years ± 2.5) were further compared against state-of-the-art clinical US (Logiq S8; GE Healthcare, Wisconsin) obtained with 11L linear transducer (GE Healthcare) carried out by an experienced vascular surgeon (C.G.S.).

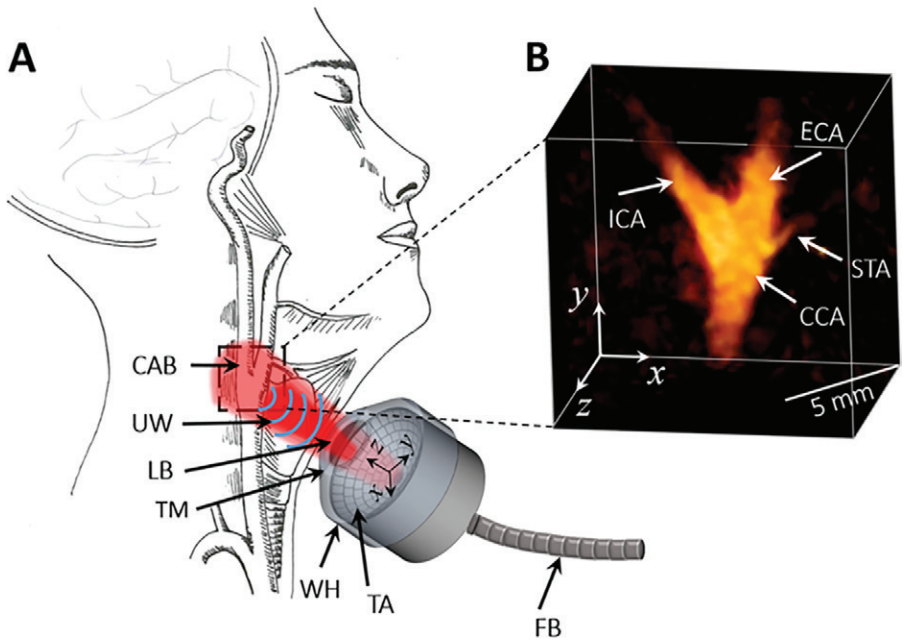

Figure 1: Images show volumetric multispectral optoacoustic tomographic (MSOT) imaging setup. *A,* Diagram illustrates handheld noninvasive scanning procedure, where volumetric MSOT probe is scanned on skin surface around carotid artery bifurcation area. *B,* Three-dimensional view of reconstructed volumetric MSOT image of carotid bifurcation captured at video rate of 10 Hz in a 44-year-old man. CAB = carotid artery bifurcation, CCA = common carotid artery, ECA = external carotid artery, FB = fiber bundle, ICA = internal carotid artery, LB = laser beam, STA = superior thyroid artery, TA = transducer array, TM = transparent membrane, UW = ultrasound waves, WH = water holder.

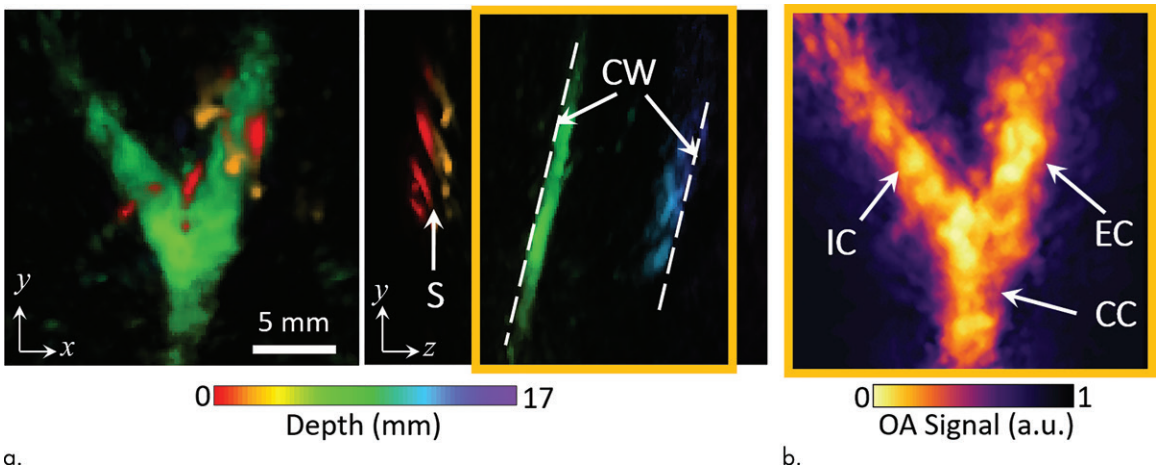

Figure 2: **(a, b)** Noninvasive volumetric multispectral optoacoustic (OA) tomographic anatomic imaging of carotid artery bifurcation in vivo in a 44-year-old man. **(a)** Image shows depth characterization. Maximum intensity projections (MIPs) of volumetric reconstructions along *z* and *y* directions are color coded to represent depth (in millimeters), where structures in red identify superficial contrast and blue and purple are indicative of deeper structures. **(b)** MIP of volumetric reconstruction of carotid bifurcation after removal of contrast arising from shallow structures. Orange box in **a** indicates depth range used for rendering MIP in **b**. CC = common carotid, CW = carotid wall, EC = external carotid, IC = internal carotid, S = skin.

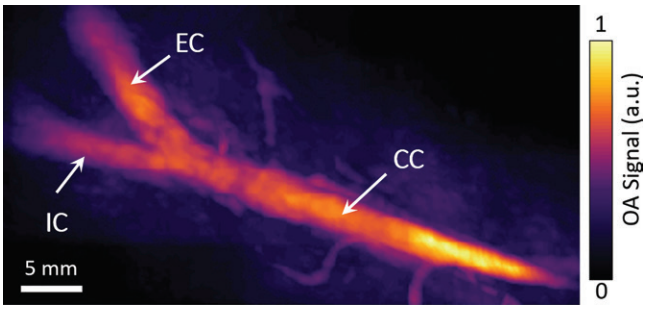

Figure 3: Compounded image of handheld volumetric multispectral optoacoustic (OA) tomography scan along entire carotid artery in a 26-year-old woman. CC = common carotid, EC = external carotid, IC = internal carotid.

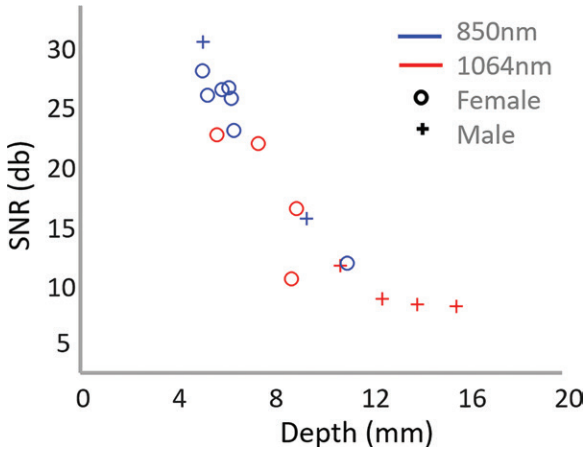

Figure 4: Graph shows signal-to-noise-ratio (SNR) of optoacoustic signal recorded noninvasively from superficial carotid wall and plotted against its depth in 16 volunteers. Measurements were performed at wavelength of either 850 nm (seven women [77.7%] with mean age ± standard deviation of 28.28 years ± 2.05; two men [22.22%] with mean age of 40.5 years ± 3.5) or 1064 nm (four women [50%] with mean age of 27.25 years ± 1.92; four men [50%] with mean age of 30 years ± 4.18).

Results

No unpleasant sensations were reported during or after the imaging sessions. The skin area was also carefully examined for any unexpected damage immediately after the sessions. No adverse effects were reported within 1 month following the scanning procedures.

We first examined the general feasibility of identifying the carotid artery bifurcation with the handheld volumetric MSOT imaging probe. Figure 1, *B* shows a perspective view of the three-dimensional tomographic reconstruction of this area acquired at a single wavelength of 850 nm from a healthy volunteer. Figure 2a shows the coronal and sagittal views color coded with depth, revealing the skin surface (red and orange), the closest carotid wall at a depth of 5–7 mm (green), and the deeper wall at a depth of 16 mm (blue). The optoacoustic signal is mainly generated by whole blood (hemoglobin) at the periphery of the vessel lumen, which allowed for clearly distinguishing the carotid walls (see *CW* in Fig 2a). The top maximum intensity projection of the captured image volume is displayed in Figure 2b, where superficial structures were removed so that the entire anatomy of the carotid bifurcation area is more clearly visible.

We further scanned an extended area spanning 45 mm along the common carotid and bifurcation by using illumination wavelength of 1064 nm. The multiple image volumes were subsequently stitched by means of a spatial compounding technique (21) to render the carotid anatomy at a larger scale (Fig 3). The scanning procedure can be best visualized in Movie E1 (online) showing three-dimensional views of the carotid bifurcation along with the common carotid artery, internal carotid artery, and external carotid artery in a single imaging session. Figure 4 summarizes optoacoustic signal decay against carotid depth in all the 16 volunteers measured at wavelengths of either 850 nm or 1064

nm. Detectable signals with signal-to-noise ratio greater than 8 dB were recorded from the carotid up to a depth of 16 mm.

Anatomic features resolved with the volumetric optoacoustic scans were validated against US images recorded from two female volunteers (mean age, 28.5 years) by using the clinical B-mode scanner (Fig 5). Although the entire carotid bifurcation area could be readily visualized with the volumetric MSOT owing to its three-dimensional imaging capabilities, it was not easily discernable in single cross-sectional US images. For instance, whereas US visualization of the whole carotid bifurcation in a single cross-section (Fig 5, *A*) required an extended acquisition time to find the suitable orientation of the US probe, a similar view could readily be obtained from the three-dimensional optoacoustic image.

Multispectral data were subsequently acquired from five healthy volunteers (three women [60%] with mean age of 26.6 years ± 3.3; two men [40%] with mean age of 40.5 years ± 3.5) at wavelengths of 730 nm, 760 nm, 800 nm, 850 nm, and 900 nm, as shown in Figure 6a. Note that the generated optoacoustic signal is affected by the wavelength-dependent light attenuation in tissues, which can be estimated by considering the hemoglobin absorption spectra (Fig 6b) (22). From a theoretical standpoint (23), for average tissue oxygenation values below 75%, such effective attenuation is expected to peak at 760 nm while having a local minimum at 800 nm (Fig 6c). It was observed that the attenuation peak at 760 nm results in a local minimum in signal (and subsequently in contrast-to-noise ratio) at this wavelength for most volunteers (n = 5), whereas a contrast-to-noise ratio peak was observed at 800 nm for some of the volunteers, arguably due to the reduced attenuation at this wavelength. It is important to consider that the optoacoustic spectrum of the carotid artery is influenced by additional factors such as the depth at which the artery is located and the presence of veins or other highly absorbing structures in the surrounding tissue. Indeed, optical properties in biologic tissues are generally heterogeneous and difficult to estimate, which hampers accurate quantification of sO_2 in vascular structures. Overall, images at longer excitation wavelengths exhibit higher contrast-to-noise ratios owing to the high oxygen saturation of the arterial blood and the corresponding trend in the oxygenated hemoglobin absorption spectrum. The measured contrast-to-noise ratio of the images in the range of 800–900 nm has a mean value of 18.8 dB ± 4.28 while having lower values of 9.18 dB ± 3.8 for shorter wavelengths of 730–760 nm (Fig 6e).

Discussion

A study was carried out to assess capabilities of the handheld volumetric multispectral optoacoustic tomography (MSOT) approach for noninvasive characterization of healthy human carotid arteries. Optoacoustic vascular imaging is associated primarily with optical absorption of blood, whose oxygenation status is spectrally distinguished through a multiwavelength imaging approach. The handheld volumetric MSOT imaging probe was devised to optimize performance of carotid imaging at centimeter-scale depths and to provide an effective field of view of approximately 2 cm^3 in real time, with the ability to scan further around the area with handheld translation of the probe. The depth of the field of view effectively captured by the transducer with respect to the skin can easily be adjusted by changing the volume of the acoustic coupling medium, up to a maximum depth of approximately 30 mm. This is generally sufficient to visualize the carotid bifurcation area in

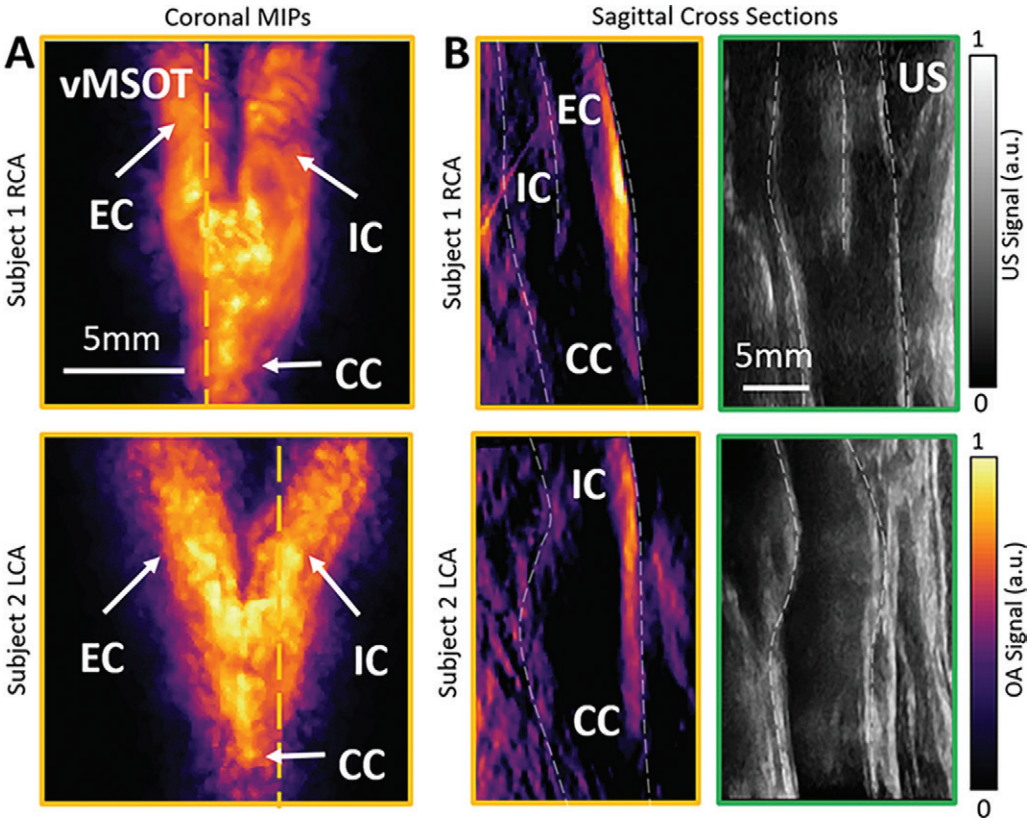

Figure 5: Images show qualitative comparison of image quality between volumetric multispectral optoacoustic tomographic (hereafter, vMSOT) and B-mode US in two volunteers. Right carotid artery (RCA) and left carotid artery (LCA) are shown in a 31-year-old woman (subject 1) and in a 26-year-old woman (subject 2), respectively. *A*, vMSOT images of carotid artery bifurcation in coronal view represented in maximum intensity projections (MIPs). *B*, vMSOT and B-mode US images of carotid bifurcation in sagittal cross-sectional views. Orange and green frames correspond to vMSOT and US images, respectively, where orange dashed lines in *A* indicate section shown in *B*. CC = common carotid, EC = external carotid, IC = internal carotid, OA = optoacoustic.

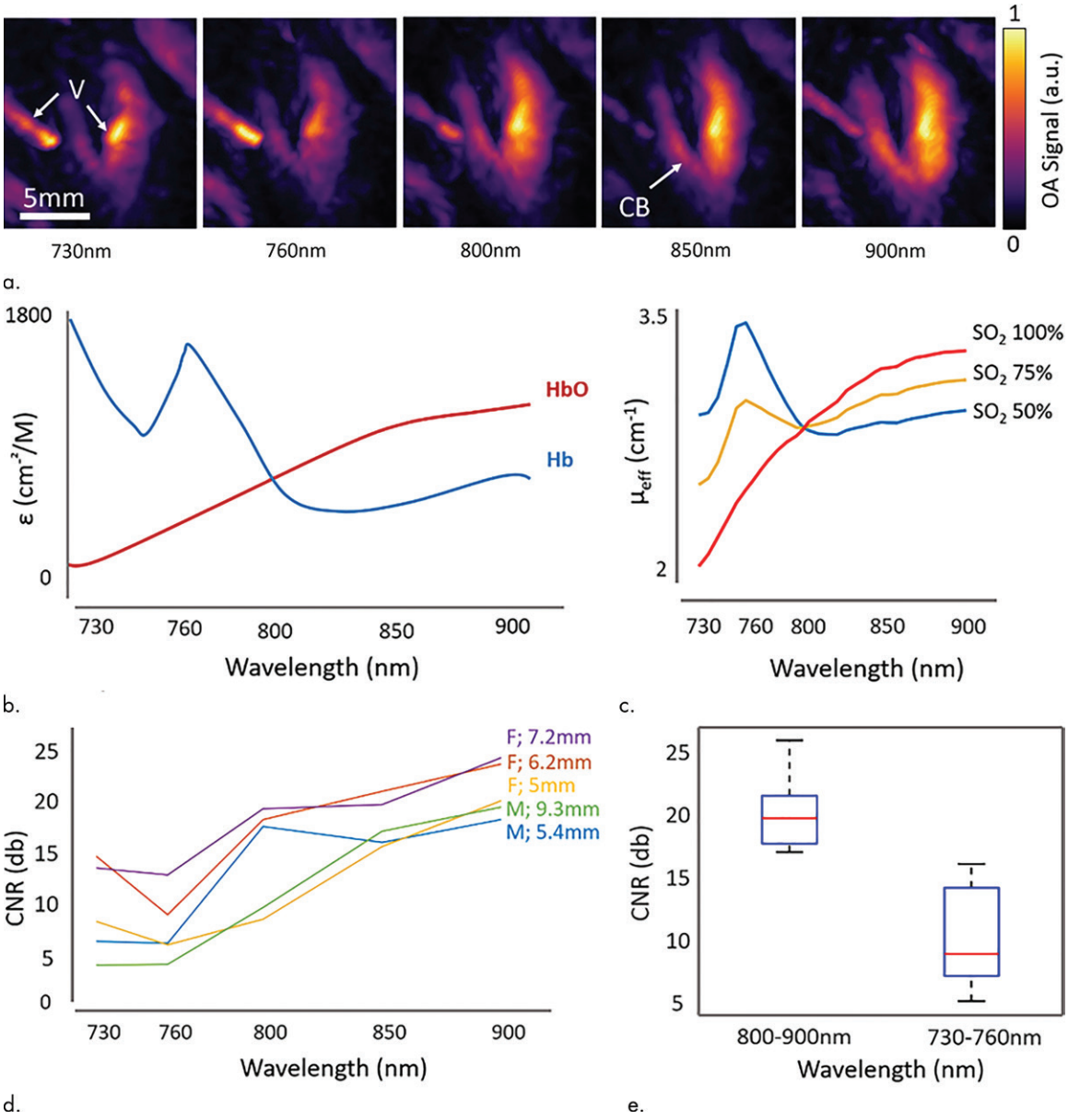

Figure 6: **(a)** Volumetric multispectral optoacoustic (OA) tomography images show right carotid artery bifurcation in a 23-year-old woman taken in wavelength range of 730–900 nm. **(b)** Graph shows spectral dependence of optical absorption by oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (Hb). **(c)** Graph shows simulated wavelength-dependent effective light attenuation coefficient of average soft living tissue. **(d)** Graph shows contrast-to-noise ratio (CNR) of images as function of wavelength including five volunteers (three of five [60%] women with mean age ± standard deviation of 26.6 years ± 3.3; two of five [40%] men with mean age of 40.5 years ± 3.5). **(e)** Graph shows statistical difference of CNR was calculated for longer wavelengths (800–900 nm) and shorter wavelengths (730–760 nm) ($P \leq .001$, *T* test). CB = carotid bifurcation, F = female, M = male, V = vein.

most patients. Light attenuation may eventually be the main factor to limit the achievable depth, even if the transducer can potentially be redesigned to be sensitive to deeper regions.

We focused on exploiting the above advantages of volumetric MSOT for imaging the carotid bifurcation, an important reference point for atherosclerotic vascular disease. Multispectral imaging was further carried out in the near-infrared window with the best image contrast from the carotid artery achieved at 1064 nm and the 800–900-nm range due to an increase of the extinction coefficient of oxygenated hemoglobin for longer wavelengths and the low light attenuation by tissues in this range. Better visibility of deeper arteries was achieved with the 1064-nm excitation, which can be ascribed to the higher per-pulse energy of the laser and weaker light attenuation at this wavelength. The spectroscopic differentiation capacity is needed for identification of other carotid artery disease biomarkers, as well as extrinsically administered targeted or activatable labels (15). Efforts in carotid plaque imaging are also geared toward noninvasive detection of vulnerable lipid-rich plaques (17,24). In this context, optoacoustic lipid detection at 1200 nm has already been demonstrated ex vivo and in preclinical intravascular studies in vivo (16,17,25). Thus, the suggested handheld volumetric MSOT approach holds promise

for rapid volumetric assessment and spectroscopic characterization of the carotid artery and plaque vulnerability in a noninvasive manner. Multispectral imaging at a more extended spectral range with proper selection of wavelengths within a broader range of 650–1250 nm can enable resolving hemoglobin, lipid, and water contributions in the optoacoustic images. To detect vulnerable plaque, the carotid artery must first be anatomically identified in single-wavelength images (eg, at 1064 nm) and once located, multispectral imaging at around 1200 nm may help to further identify lipid content, which represents a key factor in vulnerable plaques.

The real-time three-dimensional imaging capacity of volumetric MSOT presents a key advantage of the suggested handheld imaging approach pertaining to visualization of the carotid anatomy, including the common carotid artery, internal carotid artery, and external carotid artery that are simultaneously captured in a single volumetric image frame. The technique allows three-dimensional volume rendering with a single laser shot without signal averaging or probe scanning. This decreases motion-related artifacts associated with temporal and spatial blurring. In contrast, clinical US diagnostics typically rely on two-dimensional cross-sectional views where multiple alternations between the transverse and sagittal planes are necessary for comprehensive assessment of the entire region of interest.

Several limitations were encountered in this study, among which the most prominent was the lack of patient data. This prevents proper quantification of clinically relevant biomarkers (eg, lipid content) that can only be assessed after studies in patients with carotid artery disease are performed. We also note that US images may provide more detailed anatomic information in some cross-sectional views, with the underlying reason being the fundamentally different contrast delivered by the two modalities. Optoacoustics also have generally lower penetration depth due to strong light attenuation in living tissues, which may have contributed to the lack of detail from deeper tissues layers. In particular, strong light absorption by whole blood may impose additional visibility constraints (26) when imaging large blood vessels such as the carotid artery. The unique real-time volumetric imaging capacity of optoacoustics can potentially be integrated with US for a more comprehensive characterization of the carotid artery by means of a hybrid imaging probe, as was recently shown for the two-dimensional imaging case (27).

In summary, these results demonstrate the potential of volumetric multispectral optoacoustic tomography (MSOT) for spectroscopic volumetric characterization of the carotid artery in a noninvasive, real-time, and handheld manner. Volumetric MSOT is less prone to motion artifacts than are the conventional imaging methods used in clinical practice. Spectroscopic optoacoustics have the potential for label-free identification and assessment of clinically relevant biomarkers. As a result, volumetric MSOT holds promise for noninvasive functional assessment of cardiovascular disease.

Author contributions: Guarantors of integrity of entire study, I.I., E.M., D.R.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, I.I., E.M., X.L.D.B., D.R.; clinical studies, I.I.; experimental studies, all authors; statistical analysis, I.I., X.L.D.B., D.R.; and manuscript editing, I.I., E.M., X.L.D.B., D.R.

Disclosures of Conflicts of Interest: **I.I.** disclosed no relevant relationships. **E.M.** disclosed no relevant relationships. **C.G.S.** disclosed no relevant relationships. **X.L.D.B.** disclosed no relevant relationships. **D.R.** Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: has stock/stock options in iThera Medical. Other relationships: disclosed no relevant relationships.

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